Research protocol

Clin Ter 2017; 168 (5):e307-316. doi: 10.7417/T.2017.2026

The daily-practiced post-partum hemorrhage management: an Italian multidisciplinary attended protocol

G. Affronti[1], V. Agostini[2], A. Brizzi[3], L. Bucci[4], E. De Blasio[5], M.G. Frigo[6], C. Giorgini[7], M. Messina[8], A. Ragusa[9], F. Sirimarco[10], A. Svelato[9]

[1] Past direttore SC Ostetricia e Ginecologia, Ospedale S. Maria della Misericordia, AOU, Perugia; [2] UO Servizio Immunoematologia e Medicina Trasfusionale, Cesena-Forlì, Officina Trasfusionale Pievesestina; Medicina Trasfusionale Ospedale M. Bufalini, Cesena [3] Anestesia generale e locoregionale, Clinica S. Maria, Bari; [4] Anestesia e Rianimazione 1, ASST Grande Ospedale Metropolitano Niguarda, Milano; [5] UOC Anestesia e Rianimazione, Azienda Ospedaliera G. Rummo, Benevento; [6] UOS Anestesia e Rianimazione in Ostetricia, Ospedale Fatebenefratelli S. Giovanni Calibita, Roma; [7] SC Anestesia e Rianimazione, Ospedale S. Maria della Misericordia, Azienda Ospedaliero-Universitaria di Perugia; [8] Immunoematologia e medicina trasfusionale, Azienda Ospedaliera OIRM-Sant'Anna, Torino; [9] SC UO Ostetricia e ginecologia, Nuovo Ospedale delle Apuane, Massa e Carrara; [10] UO SC Ostetricia e Ginecologia, Azienda Ospedaliera Cardarelli, Napoli, Italia

Abstract

Postpartum hemorrhage (PPH) is one of the most frequent causes of mortality and morbidity in the obstetric population globally, causing about a quarter of maternal deaths yearly, and is the leading cause of maternal death worldwide. The management of PPH remains a topic of great debate, even in view of new diagnostic and therapeutic possibilities in recent years, for which, however, the body of evidence available thus far is still scarce, as the standard values are lacking.

The protocol hereby presented was developed after a literature review and during several meetings of an Italian multidisciplinary task group of specialists adopting a modified Delphi method, and is the result of the synthesis of therapeutic operational protocols for the treatment of PPH applied by the different specialties within the team.

This protocol is intended to represent a practical proposal to support clinicians in the management of a particularly complex event that requires the intervention of a multidisciplinary team and the implementation of dedicated management protocols. ***Clin Ter 2017; 168(5):e307-316?. doi: 10.7417/CT.2017.2026***

Key words: *Blood components, Postpartum hemorrhage (PPH), Protocol, Thromboelastography, Thromboelastometry, Transfusion*

Introduction

The World Health Organization defines primary postpartum hemorrhage (PPH) as blood loss greater than or equal to 500 mL within 24 hours of a vaginal delivery. PPH is regarded as severe if the blood loss exceeds 1000 mL; in a Caesarean section, blood loss equal to or greater than 1000 mL can be defined as anomalous (1). Secondary PPH is defined as abnormal bleeding from the genital tract from 24 hours after delivery until 12 weeks postpartum (2,3).

PPH is one of the most frequent causes of mortality and morbidity in the obstetric population globally, causing about a quarter of maternal deaths yearly, and is the leading cause of maternal death worldwide (1). Most deaths occur within 24-48 hours from childbirth (4). According to the latest report of the Centre for Maternal and Child Enquiries (5) on maternal mortality, despite significant improvements in the last 3 years, 66% of deaths due to PPH are still due to "substandard care"(5). PPH is also responsible for 73% of all serious morbidity during pregnancy and is the most common obstetric cause of admission to intensive care units (6).

The estimated frequency is between 5 and 22% of the total deliveries (7). In the last decade, the incidence of PPH in many industrialized countries has increased. For example, the overall rate of PPH in the United States increased by 27.5% from 1995 to 2004 (8, 9).

The causes of PPH can be manifold. In clinical practice, they are summarized as the "4Ts" (10):

- Tone (uterine atony),
- Tissue (placental problems, including retained placenta and abnormal placental implantation),
- Trauma (uterine rupture, cervical laceration, uterine inversion, or birth canal lacerations), and
- Thrombin (in relation to blood coagulation disorders due to thrombin dysfunction).

The main cause of PPH is uterine atony (9). In most cases, the bleeding occurs in the absence of evident risk factors.

The present protocol aims to propose some practical suggestions that could support the clinical management of PPH, in accordance with the knowledge and experience of experts and the various resources available in several cases in Italian hospitals. Moreover, the authors hope that each hospital service will have a massive transfusion protocol to be activated in case of critical hemorrhage with signs of hemodynamic instability and hypoperfusion (1,2,11).

Multidisciplinary hemorrhage protocols for the management of PPH have been recently advocated by many other authors (12-17), as well as professional societies, including the American College of Obstetrics and Gynecology, the UK

Correspondence: Antonio Ragusa, MD Dipartimento Materno Infantile, U.O.C. di Ginecologia e Ostetricia, Nuovo Ospedale delle Apuane, Massa e Carrara Via Aurelia, 54100, Massa Carrara. Italy. Tel.: +39 3355726903. E-mail: antonio.ragusa@gmail.com

ISSN 1972-6007

Confidential Enquiry into Maternal and Child Health, the European Society of Anaesthesiology, the French National College of Gynaecologists and Obstetricians, and The Joint Commission in the United States.

Methods

The following protocol was developed after a literature review and during several meetings of a multidisciplinary team of specialists adopting a modified Delphi method; it is the result of the synthesis of therapeutic operational protocols for the treatment of PPH applied by the different specialties within the team. Before the meetings of the experts, an extensive literature search was carried out on PubMed to identify relevant literature. These studies, together with the clinical practice of experts, were the basis for the protocol developed and the suggestions made by the Panel.

In its final version, this protocol obtained the endorsement of the Italian Association of Hospital Obstetricians and Gynecologists (AOGOI), the Association of Italian University Gynecologists (AGUI), the Italian Society of Gynecology and Obstetrics (SIGO), the Confalonieri Ragonese Foundation, and the ANEMO Association.

Management of PPH

The fundamentals of PPH treatment are: 1) maintenance of uterine contractility, obtained by physical or pharmacologic means, 2) maintenance or support of circulation with proper hydration, and 3) prevention or treatment of the established hemorrhagic coagulopathy. Intervention should be made in the "golden hour" to increase the chances of survival of the patient (2,11).

The course of treatment of a patient who experiences PPH requires the close involvement of many professionals: a specialist gynecologist, an anesthetist, a transfusionist, and an interventional radiologist. In a situation in which promptness is vital to reduce any complications in the patient, a multidisciplinary treatment plan aims to help optimize the management of the hemorrhagic event (2,5,11).

The management of PPH is still a topic of great debate, even in view of new diagnostic and therapeutic possibilities in recent years, for which, however, the body of evidence available thus far remains scarce, as are the standard values (such as the use of thromboelastometry and thromboelastography in obstetric and gynecologic settings, early supplementation with fibrinogen, and the composition of transfusion packages).

Protocol structure

The protocol proposed in the present work is based on a pragmatic approach, which allows a subdivision on two points:

Point A is regarding patients with blood losses of between 500 and 1000 mL and no signs of hemodynamic instability, for which basic monitoring measures are provided and the departments involved are alerted.

Point B is regarding patients with blood losses greater than 1000 mL and who are hemodynamically unstable, for which it is suggested that, in addition to the correction of hypoperfusion with fluids, early support of coagulation should be implemented. If available, early support of coagulation should be done by viscoelastic monitoring tools like rotational thromboelastometry (ROTEM) or thromboelastometry (TEM).

It should be highlighted that the suggested measures cannot be carried out in successive order and often need to be implemented simultaneously. In addition to the application of these measures, the knowledge and experience of the individual clinician and the team involved, which can never fail in the specific clinical situation of the patient, and the actual availability of devices and clinical or pharmacologic tools should be considered.

Figures 1 to 4 show the therapeutic measures recommended in this protocol. Unless otherwise specified, the procedures suggested are based on the 2009 Guidelines of the AOGOI (11) and the 2011 Guidelines of the Royal College of Obstetricians and Gynaecologists (2) on postpartum hemorrhage and are in accordance with the therapeutic operational protocols developed at their hospitals by the authors.

It must be made sure that the patient is not suffering from inherited coagulation disorders: prophylaxis and relevant treatment, in case of congenital coagulation dysfunctions, must be agreed with the hematologist who is in charge of the patient, and put in place following the appropriate guidelines. The expert group decided to exclude patients with inherited bleeding disorders from this sum of suggestions.

Point a: blood losses between 500 and 1000 ml with no signs of hemodynamic instability (Fig. 1)

The first action to be taken in case of PPH is to request the cooperation of other medical and paramedic staff, such as a gynecologist and a second expert obstetrician. It is also advisable to alert the anesthetist, as well as the transfusion center (where available), operating room, vascular surgery department, and possibly other nursing staff; where available, the interventional radiology department should also be alerted.

While waiting for support, an assessment of the extent of the bleeding through retroplacental bag, gauze, and drapes is advised. The literature provides evidence that an accurate estimate of blood loss can shorten the transfusion time, thereby reducing the severity of the hemorrhage (12). Obtaining an accurate assessment of blood loss is a well-known problem, and many authors have highlighted the importance of appropriate and periodically repeated training in this regard (13). We are in agreement on this issue, calling for the implementation of a dedicated program of training and continuing education for all obstetrics staff.

Simultaneous with the assessment of blood loss is the need to begin the monitoring of vital signs: blood pressure, respiratory rate, heart rate, electrocardiography (ECG), pulse oximetry, temperature, and diuresis through a urinary catheter. Checking should be done initially every 10 minutes, according to the clinical evolution, and then every 30 minutes. It is useful to record the progress of the vital signs on suitable predesigned graphic sheets, if possible; this allows for fast verification of the data trend, even in an emergency (12). At this stage,a request for blood components should be sent to the transfusion center.

ASK FOR HELP Ask for the assistance of other professionals such as a gynecologist, a second expert obstetrician. Alert the anesthetist, Transfusion Center, operating room, vascular surgery and interventional radiology departments (where available). Involve staff with more experience
↓
ENSURE VENOUS ACCESS Place urinary catheter and ensure two venous access points through a cannula of 16G or 14G
↓
BLOOD SAMPLES Take samples per group and repeated checks of blood count, PT, PTT, fibrinogen (Clauss), AT BLOOD REQUEST Request for 4 units of RBC and available plasma POC TEST Where available
↓
ASSESS BLOOD LOSSES AND HEMODYNAMIC INSTABILITY Assess the extent of the bleeding and the patient's vital signs every 10-30 minutes (blood pressure, respiratory rate, heart rate, ECG, arterial oxygen saturation, temperature, urine output through a urinary catheter) Record the values of the vital signs on graphics sheets
↓
PHARMACOLOGICAL THERAPY Increase the oxytocin dose by prophylactic therapy (20 IU in 500 mL of saline in 2 hours); if after 20 minutes there is no effect, use a second-line uterotonic. Administer tranexamic acid (30 mg / kg ABW)
↓
AVOID HYPOTHERMIA, ACIDOSIS (LACTATES > 2 mmol/L, DESATURATION
↓
ESTABLISH ORIGIN OF BLEEDING AND CORRECTIVE ACTIONS Apply the rule of the 4 Ts (TONE, TISSUE, TRAUMA, THROMBIN)
TONE (uterine atony) Bimanual compression of the uterus, intrauterine tamponade with balloon catheter, uterotonic medicine **THROMBIN** Correct any coagulation defects with fresh frozen plasma and specific concentrates, possibly guided by thromboelastometry
TISSUE Exploration and evacuation of uterus **TRAUMA** Repair of lacerations of the birth canal
↓
NO RESPONSE → GO TO POINT B

ABW = Adjusted Body Weight; AT = Antithrombin; ECG = Electrocardiography; IU = International Unit; PT = Prothrombin Time; PTT = Partial Thromboplastin Time; RBC = Red Blood Cells

Fig.1. Protocol: Point A. Management of PPH in case of blood losses between 500 and 1000 mL with no signs of hemodynamic instability.

The patient's two large venous access points (16 G or, better, 14 G) should also be established to clearly separate the route of administration of oxytocics from that of infusions needed to support the blood volume; the use of infusion pumps is preferable. A urinary catheter also needs to be inserted to empty the bladder.

The pharmacologic therapy at this stage includes oxytocin and tranexamic acid (TXA). There is significant variation in practice in this regard. However, a systematic review of all the available uterotonics for the prevention of PPH has found oxytocin to be the first choice, and a recent Cochrane review supported this recommendation (3). According to the Panel, the dose of oxytocin should be increased to switch from prophylaxis to therapy (20 IU in 500 mL saline in 2 hours): if no effect is observed after 20 minutes, a second-line uterotonic may have to be given according to the clinical situation of the patient.

Evidence supporting the early use of TXA in massive hemorrhage has been rapidly increasing. The efficacy of such therapy in decreasing blood loss and transfusion requirements in vaginal and caesarean deliveries has been previously confirmed (12,13). In a recent prospective trial, a significant reduction of secondary measures was found in severe PPH treated with tranexamic acid (18).

A recent systematic review with meta-analysis recommended caution in the use of tranexamic acid in the pro-

phylaxis of postpartum hemorrhage (19). However, current knowledge indicates that the levels of fibrinogen are higher in pregnant than in non pregnant women. The levels increase considerably in the third quarter of pregnancy, in relation to the estrogen levels (20), and then decrease after the expulsion of the placenta (after birth) due to intravascular fibrin deposition postpartum, which results in increased consumption of fibrinogen (18). In fact, electron microscopy studies of placental bed tissue biopsies have shown that immediately after a normal birth, an extravascular fibrin "wallpaper" appears on the endometrial surface (21).

According to these mechanisms, TXA, as an antifibrinolytic agent, can be assumed to be an effective therapy to control EPP (18,20). Therapeutic inhibition of fibrinolysis has already proven to be effective in reducing the bleeding in various clinical situations associated with activation and dysregulation of the fibrinolytic system, including cardiac, hepatic, trauma, neurosurgical, and obstetric settings (22). A randomized, multicenter study carried out in 2011 on 144 patients showed that the use of high-dose tranexamic acid (4 g) significantly reduced the amount of blood loss (PPH defined as blood loss > 800 ml after vaginal delivery), the duration of blood loss, and the need for transfusions and invasive procedures, in the absence of side effects, except for two cases of thrombosis in the group treated with TXA (18). The CRASH 2 study showed that in a trauma patient, the administration of TXA at high doses (loading dose of 1g during 10 minutes followed by an infusion of 1g during 8 hours) reduced all-cause mortality from 16% to 14.5% within 4 weeks, with no increase in thrombotic events. Furthermore, this trial showed that the benefit on survival was evident only if the TXA treatment was started within 3 hours after injury, without increasing the risk of cardiovascular occlusive events (23).

The data suggest that TXA should be given at a dose of 30 mg/kg adjusted body weight (ABW). Obese patients can have an excess of 30% fat; thus, the adjusted body weight helps account for the change, assuming 40% of lean mass and 60% of fat mass for anything above the ideal body weight.

At the same time, samples for blood group have to be taken, and repeated blood counts and basic coagulation tests should be carried out: prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen (with the Clauss method), and antithrombin (AT).

AT monitoring is relevant in clinical situations with ongoing bleeding. A decrease in AT may be associated with an increased risk of thrombosis; however, there is no evidence that normal AT levels decrease the thrombotic risks associated with rFVIIa administration. We point out

the importance of not given AT during the acute bleeding phase due to the potential risk of worsening coagulopathy (24). Thus far, there are no data available on the stepwise changes in the concentration of AT during the bleeding event. In all likelihood, PPH patients may experience an ongoing decrease comparable with that in trauma patients (24).

Close monitoring is needed to avoid or correct hypothermia and to measure and avoid acidosis (lactates > 2 mmol / L) and desaturation. We suggest that an arterial blood gas analysis be carried out to obtain a baseline hemoglobin level (which is useful for the subsequent monitoring of blood loss), as well as estimation of the arterial oxygen saturation combined with pulse oximetry.

For a correct diagnostic and therapeutic overview of the patient, the source of bleeding should be established by applying the rule of the 4 Ts (10), and the relevant corrective actions should be determined:

TONE (bimanual uterine compression, intracavitary uterine tamponade through a hydrostatic balloon catheter, and use of uterotonics). In the absence of a hydrostatic balloon, a latex glove or a condom can be used with good results, as suggested by the FIGO 2012 Guidelines (25). It should be emphasized that the use of gauze tamponade is now discouraged.

TISSUE (exploration and evacuation of the uterus).

TRAUMA (vaginal lacerations and cervix and/or uterine rupture repair).

THROMBIN (in relation to blood coagulation disorders due to thrombin dysfunction; any coagulation defects should be evaluated and corrected with ROTEM/TEG monitoring, if available).

Point b: blood losses > 1000 ml in patients with hemodynamic instability (Figs.. 2-4)

The transition to Point B should be made only when resolution of the effective hemorrhage is not achieved after all the operations referred to in Point A have been put in place. The first procedure referred to in Point B (Fig. 2) is the restoration of the circulating volume by giving the least volume of crystalloids (Ringer-lactate/acetate as the first line) or colloids (26) until the hypoperfusionis corrected, based on an evaluation of the clinical and laboratory variables (sensory state, diuresis, lactates, and deficit base), and hasten the request of blood products. In the administration of colloids, it is crucial to consider the information note issued by the AIFA and the EMA in December 2013 regarding restrictions on the use of medicines containing hydroxyethyl starch (HES) (26).

Then, the path of the protocol is differentiated according to the availability or nonavailability of a POC monitoring tool in the structure that has taken charge of the patient (Figs. 2-4). For both arms of the protocol, the use of warming devices and rapid infusers is appropriate, and the basic conditions should always be ensured: hematocrit > 21%, temperature > 34 °C, pH > 7.20, and Ca++> 1 mmol/L.

In addition to the assessment of coagulation by laboratory standard tests, Point-of-Care (POC) testing should be done, if available. TEG/ROTEM are capable of providing a useful assessment of the coagulation status within minutes. There are numerous case reports of the use of TEG and ROTEM to guide the replacement of blood components in the management of PPH, and studies have confirmed a reduction in blood loss and associated transfusion of blood products with the use of these tests in other settings (13). A strong correlation has been identified between standard coagulation variables and ROTEM variables in women shortly after delivery (27,28).

The FIBTEM is a ROTEM assay that evaluates the fibrinogen component and seems to be well correlated with the standard laboratory fibrinogen levels (29). There is strong evidence that the ROTEM FIBTEM A5 assay can be used as a surrogate for Clauss fibrinogen during PPH. It should be noted that this assay does not measure the same hemostatic

PERFORM ALL ACTIONS PROVIDED IN POINT A

↓

HYPOPERFUSION CORRECTION
Infuse crystalloid (first line) or colloids while waiting for blood
Assess the sensory state, base excess, lactates, urine output

↓

ADMINISTER OXYGEN

↓

TRANSFUSION THERAPY

Always ensure the basic conditions:
hematocrit > 21%, temperature > 34 °C, pH > 7.20, Ca^{++}> 1 mmol / L

If infusion rate > 50 mL / kg / h:
use warmers and rapid infusers

Is Point of Care (ROTEM / TEG) monitoring available?

NO	**YES**
"BLIND" TRANSFUSION THERAPY While waiting for the laboratory results – 4 bags of packed red blood cells: 4 units of plasma from a single donor or industrial type – or 4 bags of packed red blood cells: 2 units of apheresis plasma – Platelet concentrate, 1 unit of apheresis or buffy coat per 8 bags of packed red blood cells If PTT or INR > 1.5: transfuse packed red blood cells and plasma (starting dose 20 ml / kg, up to 30 ml / kg for persistent or worsening coagulopathy) If fibrinogen (Clauss or ROTEM / TEG) ≤ 200 mg / dL, the infusion of the following is recommended: – fibrinogen concentrate (30-50 mg / kg) or – cryoprecipitate (1 unit per 10 kg)	**TRANSFUSION THERAPY GUIDED** BY ROTEM (see Fig. 3) OR BY TEG (see Fig. 4)

↓

NO RESPONSE

↓

PREVENT OUTBREAK OF DIC
Treat the underlying cause (persistent hemorrhage, shock, hypothermia, acidosis) and establish appropriate haemodynamic support

↓

NO RESPONSE

↓

CONSERVATIVE SURGERY AND INTERVENTIONAL RADIOLOGY
Compression sutures (B-Lynch, Hayman), devascularisation (uterine, ovarian or internal iliac arteries), selective embolisation of pelvic vessels

↓

NO RESPONSE

↓

OFF-LABEL USE OF rFVIIa
Bolus of 60-90 µg / kg may be repeated within 15-30 mins

↓

NO RESPONSE

↓

SUBTOTAL OR TOTAL HYSTERECTOMY

DIC = Disseminated intravascular coagulation; INR = International Normalized Ratio; PTT = Partial Thromboplastin Time; rFVIIa = Recombinant factor VIIa

Fig. 2. Protocol: Point B. Management of PPH in case of blood losses > 1000 mL, for a patient with hemodynamic instability

variable that Clauss fibrinogen does but rather provides similar measures of hemostatic competence (14). Some studies have reported that even the TEG-based functional fibrinogen (FF) assay correlates well with the standard von Clauss fibrinogen assay (30,31).

During massive hemorrhage, fibrinogen is one of the first coagulation factors to decrease beyond critical levels. Term pregnant women have an increased concentration of fibrinogen of approximately 4.5-5.8 g/l compared with the normal value of 2.0-4.5 g/l (32). Several recent studies have suggested that fibrinogen is an important predictor of severe PPH (33-37). Some guidelines have indicated that fibrinogen concentrate should be the replacement therapy of choice (38,39); however, evidence from clinical trials is still scarce. Currently, some randomized controlled studies are being done to provide better insight into the early use of fibrinogen concentrate in PPH (40-43).

Coagulation monitoring can be done by using ROTEM or TEG viscoelastic tests. Thus, we present both guided ROTEM therapy (Fig. 3) and guided TEGtherapy (Fig. 4).

Thus far, no reference values for monitoring by POC testing in obstetric and gynecologic settings have been standardized and shared (28,44,45). Therefore, our suggestions are only indicative to support the decisions of the specialists involved. The information presented herein is not intended to replace the assessment of individual physicians, who base their decisions on the clinical situation of the single patient, according to protocols established by the structure applied and the availability of equipment and blood components.

We consider it appropriate to suggest indications regarding the interpretation of the viscoelastic variables, which may constitute an indicative support in clinical practice.

If POC testing is not available, transfusion in the presence of the effective PPH is done based on clinical indications and not on information obtained from blood chemistry tests (Fig. 2, "blind transfusion therapy"). Therefore, it should be noted that a bag of packed red blood cells contains 280 ml and increases the hematocrit level by 2-3%. When more than 3 or 4 bags have been transfused rapidly, a blood warmer should be used.

There are currently two practices applied in massive hemorrhage: fixed product ratio or individualized procoagulant intervention and factor substitution (39). Patients transfused with a high ratio of red blood cells (RBC) to fresh frozen plasma (FFP) of >1:2 seem to have lower mortality (16,46). In the absence of laboratory information and in case of severe PPH (blood loss > 1000 mL in a hemodynamically unstable patient), we suggest the use of a bag of plasma and platelets for each bag of packed red blood cells while waiting for laboratory values. Regarding the package to be transfused, the following alternative ratios are suggested according to the availability of blood components: 4 bags of packed red blood cells to 4 units of plasma from a single donor or industrial type, or 4 bags of packed red blood cells to 2 units of apheresis plasma. For platelet concentrates, the use of 1 unit by apheresis or buffy coat for every 8 bags of packed red blood cells is suggested.

Emphasis should be given to the suggestive character of the above alternatives, which are not to be considered as recommendations, and the application of which in clinical practice may vary given the uneven distribution and availability of blood components and monitoring equipment.

Long EXTEM CT →	FFP 20-30 ml/kg	
EXTEM ML > 15% →	Normal APTEM →	TXA 1 g
EXTEM A10 < 40 mm →	FIBTEM A5 ≤ 6 mm or A15 ≤ 8 mm→	Fibrinogen concentrate 2-4 g
	FIBTEM A5 ≥ 6 mm or A15 ≥ 8 mm→	Platelet concentrate
→ NO RESPONSE		
→ GO BACK TO FIGURE 2		

A10 = Clot firmness (mm) 10 minutes after CT; A5 = Clot firmness (mm) 5 minutes after CT; CT = Clotting time; FFP = Fresh Frozen Plasma; ML = Maximum lysis; TXA = Tranexamic acid

Fig. 3. Protocol: Point B. Transfusion therapy guided by ROTEM

Administer PLT Monitor coagulation: repeat INR, PPT, fibrinogen, PLT and TEG every 60-90 minutes Possible request for additional blood products				
R > 1 →	Deficiency of coagulation factors→	Plasma / Cryoprecipitate		
R > 0 < 1 → MA > 54 < 72 →	Surgical bleeding →	Experienced surgeon		
MA < 54 →	Functional fibrinogen (FF) →	MA > 9 < 29 →	Shortage of platelets →	Platelets
		MA < 9→	Deficiency of fibrinogen →	Fibrinogen
→ NO RESPONSE				
→ GO BACK TO FIGURE 2				

INR = International Normalized Ratio; PTL = Platelets

Fig. 4. Protocol: Point B. Transfusion therapy guided by TEG [rapid TEG (r-TEG)]

It is also desirable that each hospital draw up a massive transfusion protocol to be activated in case of critical hemorrhage with signs of hemodynamic instability and hypoperfusion.

When the results of coagulation tests are available, if the prothrombin time ratio (PTTr) or international normalized ratio (INR) is > 1.5, the Panel suggests infusing plasma, at the same time as the packed red blood cells, at an initial dose of 20 ml/kg and up to a dose of 30 ml/kg in case of persistent or worsening coagulopathy. In cases of altered coagulation, the epidural catheter, which is used during labor, should be left in place until the coagulation level has been normalized.

One of the leading causes of death due to PPH in the Western world is delay in the administration of blood. For example, in a multicenter study carried out in France by Bonnet et al., the time elapsed from the start of PPH to the first transfusion was correlated with the severity of the outcome and mortality: 82 minutes before transfusion for deceased patient scompared with a much shorter time for survivors (47).

Considering the rapid decrease of fibrinogen in hemodynamically unstable patients with severe PPH, if the values of fibrinogen, detected by the Clauss method or thrombelastometry/thromboelastography, are less than or equal to 200 mg/dL, we suggest early supplementation with fibrinogen concentrate (30 mg/kg) or cryoprecipitate (1 unit/10 kg of body weight), although this procedure has recently been considered a second-line treatment, with a degree of evidence of 3-I.

Cases that do not respond to the therapies described above require a conservative surgical interventionist approach: balloon tamponade (56); compression sutures (B-Lynch/Hayman), possibly by using "the sandwich effect" (combination of compression sutures with a hydrostatic balloon) (25,48,49) combining devascularization sutures of the uterine, ovarian, and internal iliac arteries; and selective embolization of the pelvic vessels, such as the uterine and cervicovaginal arteries.

The administration of the recombinant activated factor VII (rFVIIa) is somewhat controversial: rFVIIa has been used empirically during obstetric hemorrhage as a last-ditch attempt to prevent hysterectomy, with anecdotal evidence of success (13); however,it is not currently recommended for routine treatment of PPH due to its heavy thrombotic risks (50). If there is no response to the previous measures, the administration of rFVIIa at a dose of a bolus of 60-90 mg/kg can be suggested; this may be repeated within 15-30 minutes as a last resort before hysterectomy. It should be noted, however, that the effectiveness of rFVIIa depends on the values of some basic variables, such as pH, temperature, platelet count (> 50,000/mm^3), and fibrinogen level (> 200 mg/dL).

In case of nonresponse to the measures outlined thus far, the application of subtotal or total hysterectomy will be necessary. This decision should be made by the most experienced obstetrician and preferably supported by a second experienced clinician. Subtotal hysterectomy has lower surgical morbidity and is the operation of choice, unless there is trauma to the cervix or lower segment (grade 2-IIb/2-III) (12).

If the cervix and paracolpos are not involved as the source of hemorrhage, subtotal hysterectomy should be adequate to achieve hemostasis, which is the objective of the intervention. Additionally,the procedure is safer, faster, easier to carry out, and less likely to injure the bladder or ureters compared with total hysterectomy (1,51). However, if the lower segment and paracolpos are involved in the hemorrhage, such as in cases of placenta previa, total hysterectomy will be necessary for hemostasis (1,51).

Conclusion

There are still many critical points in the management of PPH, starting from the difficulty of properly assessing the extent of the bleeding, and these could dangerously affect the timeliness of diagnosis and corrective and/or therapeutic actions. Delay in initiating appropriate management of PPH is the main factor associated with adverse outcomes:the most important measure at diagnosis of PPH is that immediate action should be taken in the "golden hour" to ensure the best chance of preserving organ function and preventing maternal death.

Another critical point is the involvement of a multidisciplinary team that has the necessary tools to operate at its bestand whose members interact competently and promptly. In this sense, the availability of blood products and tools to monitor coagulation is necessary. Unfortunately, because not all hospitals have the same equipment and supplies, this can become a critical issue.

The introduction of thromboelastography and thromboelastometry constitutes an important innovation in the diagnosis of coagulopathy and the management of blood transfusion in cardiac, liver, and trauma settings. The relevant literature shows a good connection between the results of thromboelastometry/thromboelastography and those of the traditional coagulation tests, and in non-gynecologic settings, POC monitoring is a rather common practice (52-55). However, data on the use of POC monitoring in obstetric and gynecologic emergencies are still limited and therefore require further study and analysis (28,44,45).

The authors developed the protocol presented here because of the complex situations they encounter in their daily clinical practice, for which the evidence is scarce and expert opinions are relied on. The importance of this protocol lies in the practical information suggested, which can support clinicians in addressing problems related to PPH in clinical practice. Moreover, the authors hope to stimulate debate and direct attention to the need to develop dedicated protocols for PPH management.

Acknowledgments

The authors thank Dr. Agostini and Dr. Brizzi for allowing the use of the PPH protocols developed at their respective hospitals,as shown in Figs. 3 and 4 of this report, and Dr. Danilo Celleno, Prof. Gian Carlo Di Renzo, and Dr. Elvira Grandone for their advice. Editorial assistance was provided by SEEd Medical Publisher, in the person of Rossella Iannone.

This project was supported by CSL Behring S.p.A with an unconditional grant. The funder had no role in the collection, analysis, or interpretation of data.

Disclosure of conflict of interest

Dr. Affronti declares a financial relationship with Cook Medical Europe, Dr. De Blasio and Dr. Giorgini declare no financial relationship.

Dr. Brizzi, Dr. Bucci, Dr. Frigo, Dr. Ragusa, Dr. Sirimarco, and Dr. Svelato declare a financial relationship with CSL Behring.

Dr. Messina declares a financial relationship with CSL Behring, Bayer, Novo Nordisk, Baxter, Pfizer.

Dr. Agostini declares a financial relationship with Novo Nordisk.

References

1. WHO recommendations for the prevention and treatment of postpartum haemorrhage. 2012. Available at: http://apps.who.int/iris/bitstream/10665/75411/1/9789241548502_eng.pdf (Last accessed 15 December 2016)
2. Royal College of Obstetricians and Gynaecologists (RCOG). Prevention and management of postpartum haemorrhage. Green-top Guideline N. 52. 2009 Available at: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg52/ (Last accessed 15 December 2016)
3. Mousa HA, Blum J, Abou El Senoun G, et al. Treatment for primary postpartum haemorrhage. Cochrane Database Syst Rev 2014 Feb 13;2:CD003249. http://dx.doi.org/10.1002/14651858.CD003249.pub3
4. Hogan MC, Foreman KJ, Naghavi M, et al. Maternal mortality for 181 countries, 1980-2008: A systematic analysis of progress towards Millennium Development Goal 5. Lancet 2010;375:1609-23. http://dx.doi.org/10.1016/S0140-6736(10)60518-1
5. Cantwell R, Clutton-Brock T, Cooper G, et al. Saving Mothers' Lives: reviewing maternal deaths to make motherhood safer: 2006-08. The Eighth Report on Confidential Enquiries into Maternal Deaths in the United Kingdom. BJOG 2011;118 Suppl 1:1-203. http://dx.doi.org/10.1111/j.1471-0528.2010.02847.x
6. Lennox C, Marr L. Scottish confidential audit of severe maternal morbidity: reducing avoidable harm. Ninth Annual Report. Healthcare Improvement Scotland, 2013. Available at: http://www.scottishpatientsafetyprogramme.scot.nhs.uk/Media/Docs/MCQIC/Maternity%20Care/2013-08-09%20Final%209th%20annual%20SCASMM%20report.pdf (Last accessed 15 December 2016)
7. Rogers S, Chang AMZ. Postpartum hemorrhage and other problems of the third stage. In: James DK, Steer PJ, Weiner CP, Gonik B (eds). High Risk Pregnancy. Management options. Philadelphia. ElsevierSaunders, 2006; pp 1559-1578
8. Knight M, Callaghan WM, Berg C, et al. Trends in postpartum hemorrhage in high resource countries: a review and recommendations from the international postpartum hemorrhage collaborative group. BMC Pregnancy Childbirth 2009; 9: 55. http://dx.doi.org/10.1186/1471-2393-9-55
9. Bateman BT, Berman MF, Riley LE, et al. The epidemiology of post partum hemorrhage in a large, nationwide sample of deliveries. AnesthAnalg 2010;110:1368-73. http://dx.doi.org/10.1213/ANE.0b013e3181d74898
10. Mukherjee S, Sabaratnam A. Post-partum haemorrhage. Obstetrics, Gynaecology and Reproductive Medicine 2009; 19: 121-16. http://dx.doi.org/10.1016/j.ogrm.2009.01.005
11. Meir JY, Natale N, Arisi E, et al.Emorragia post-partum: linee guida per la prevenzione, la diagnosi e il trattamento. Linee guida AOGOI. 2009. I libri dell'AOGOI. Cento (Ferrara): Editeam; pp 23-49
12. Abdul-Kadir R, McLintock C, Ducloy AS, et al.Evaluation and management of postpartum hemorrhage: consensus from an international expert panel. Transfusion 2014;7: 1756-68. http://dx.doi.org/10.1111/trf.12550
13. Pavord S, Maybury H. How I treat postpartum hemorrhage. Blood 2015;125:2759-70. http://dx.doi.org/10.1182/blood-2014-10-512608
14. Collins P, Abdul-Kadir R, Thachil J; Subcommittees on Women' s Health Issues in Thrombosis and Haemostasis and on Disseminated Intravascular Coagulation. Management of coagulopathy associated with postpartum hemorrhage: guidance from the SSC of the ISTH. J ThrombHaemost 2016;14:205-10. http://dx.doi.org/10.1111/jth.13174
15. Mallaiah S, Barclay P, Harrod I, et al. Introduction of an algorithm for ROTEM-guided fibrinogen concentrate administration in major obstetric haemorrhage. Anaesthesia 2015;70:166-75. http://dx.doi.org/10.1111/anae.12859
16. Girard T, Mörtl M, Schlembach D.New approaches to obstetric hemorrhage: the postpartum hemorrhage consensus algorithm. CurrOpinAnaesthesiol 2014;27:267-74. http://dx.doi.org/10.1097/ACO.0000000000000081
17. Butwick AJ, Goodnough LT. Transfusion and coagulation management in major obstetric hemorrhage. CurrOpinAnaesthesiol 2015;28:275-84. http://dx.doi.org/10.1097/ACO.0000000000000180.
18. Ducloy-Bouthors AS, Jude B, Duhamel A, et al; EXADELI Study Group, Susen S. High-dose tranexamic acid reduces blood loss in postpartum haemorrhage. Crit Care 2011;15:R117. http://dx.doi.org/10.1186/cc10143
19. Sentilhes L, Deneux-Tharaux C. Prophylactic tranexamic acid in addition to uterotonics may prevent blood loss for vaginal and caesarean deliveries. Evid Based Med 2016;21:97. http://dx.doi.org/10.1136/ebmed-2016-110382
20. Butwick AJ.Postpartum hemorrhage and low fibrinogen levels: the past, present and future. Int J ObstetAnesth 2013;22:87-91. http://dx.doi.org/10.1016/j.ijoa.2013.01.002
21. Ludwig H. Surface structure of the human term placenta and of the uterine wall post partum in the screen scan electron microscope. Am J ObstetGynecol 1971;111:328-44
22. Movafegh A, Eslamian L, Dorabadi A. Effect of intravenous tranexamic acid administration on blood loss during and after cesarean delivery. Int J GynaecolObstet 2011;115:224-6. http://dx.doi.org/10.1016/j.ijgo.2011.07.015
23. Edwards P, Shakur H, Barnetson L, et al. Central and statistical data monitoring in the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2) trial. Clin Trials 2014;11:336-343
24. Schoechl H, Voelckel W, Maegele M, et al. Endogenous thrombin potential following hemostatic therapy with 4-factor prothrombin complex concentrate: a 7-day observational study of trauma patients. Crit Care 2014;18:R147. http://dx.doi.org/10.1186/cc13982
25. Lalonde A; International Federation of Gynecology and Obstetrics. Prevention and treatment of postpartum hemorrhage in low-resource settings. Int J GynaecolObstet 2012;117:108-

18. http://dx.doi.org/10.1016/j.ijgo.2012.03.001
26. AIFA.Nota informativa importante concordata con l'EMA e l'AIFA: Restrizione d'uso di HES (medicinali contenenti amido idrossietilico). 2013. Available at: http://www.agenziafarmaco.gov.it/it/content/nota-informativa-importante-sulla-restrizione-d%E2%80%99uso-di-hes-medicinali-contenenti-amido-idros (Last accessed 15December 2016)
27. Oudghiri M, Keita H, Kouamou E, et al. Reference values for rotation thromboelastometry (ROTEM®) parameters following non-haemorrhagic deliveries. Correlations with standard haemostasis parameters. ThrombHaemost 2011;106:176-8. http://dx.doi.org/10.1160/TH11-02-0058
28. de Lange NM, van Rheenen-Flach LE, Lancé MD, et al. 2014. Peri-partum reference ranges for ROTEM(R) thromboelastometry. Br J Anaesth 2014;112:852-9. http://dx.doi.org/10.1093/bja/aet480
29. Huissoud C, Carrabin N, Audibert F, et al. Bedside assessment of fibrinogen level in postpartum haemorrhage by thrombelastometry. BJOG 2009;116:1097-102. http://dx.doi.org/10.1111/j.1471-0528.2009.02187.x
30. Solomon C, Collis RE, Collins PW. Haemostatic monitoring during postpartum haemorrhage and implications for management. Br J Anaesth 2012;109:851-63.http://dx.doi.org/10.1093/bja/aes361
31. Harr JN, Moore EE, Ghasabyan A, et al. Functional fibrinogen assay indicates that fibrinogen is critical in correcting abnormal clot strength following trauma. Shock 2013; 39:45-9. http://dx.doi.org/10.1097/SHK.0b013e3182787122
32. Levy JH, Welsby I, Goodnough LT. Fibrinogen as a therapeutic target for bleeding: a review of critical levels and replacement therapy. Transfusion2014;54:1389-405; http://dx.doi.org/10.1111/trf.12431
33. Charbit B, Mandelbrot L, Samain E, et al; PPH Study Group. The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. J ThrombHaemost 2007; 5:266–273
34. Cortet M, Deneux-Tharaux C, Dupont C, et al. Association between fibrinogen level and severity of postpartum haemorrhage: secondary analysis of a prospective trial. Br J Anaesth 2012;108:984-9.http://dx.doi.org/10.1093/bja/aes096
35. Gayat E, Resche-Rigon M, Morel O, et al. Predictive factors of advanced interventional procedures in a multicentre severe postpartum haemorrhage study. Intensive Care Med 2011;37:1816-25. http://dx.doi.org/10.1007/s00134-011-2315-0
36. de Lloyd L, Bovington R, Kaye A, et al. Standard haemostatic tests following major obstetric haemorrhage. Int J ObstetAnesth 2011;20:135-41. http://dx.doi.org/10.1016/j.ijoa.2010.12.002
37. Collins PW, Lilley G, Bruynseels D, et al. Fibrin-based clot formation an early and rapidly available biomarker for progression of postpartum hemorrhage: a prospective cohort study. Blood 2014;124:1727-36. http://dx.doi.org/10.1182/blood-2014-04-567891
38. Swedish Society on Thrombosis and Haemostasis (SSTH). Haemostasis in cases of severe haemorrhage: a treatment programme developed by a work group of the Swedish Society on Thrombosis and Haemostasis. 2010. Available at: http://www.skane.se/upload/Webbplatser/UMAS/VERKSAMHETER%20UMAS/Hemostas2_web-linked,%20110325%20final.pdf. (Last accessed 25 February 2016)
39. Kozek-Langenecker SA, Afshari A, Albaladejo P, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. Eur J Anaesthesiol 2013;30:270-382. http://dx.doi.org/10.1097/EJA.0b013e32835f4d5b
40. Wikkelsoe AJ, Afshari A, Stensballe J, et al. The FIB-PPH trial: fibrinogen concentrate as initial treatment for postpartum haemorrhage: study protocol for a randomised controlled trial. Trials 2012;13:110. http://dx.doi.org/10.1186/1745-6215-13-110
41. Wikkelsoe AJ, Edwards HM, Afshari A, et al; FIB-PPH trial group. Pre-emptive treatment with fibrinogen concentrate for postpartum haemorrhage: randomized controlled trial. Br J Anaesth 2015;114:623-33. http://dx.doi.org/10.1093/bja/aeu444
42. Aawar N,Alikhan R, Bruynseels D, et al. Fibrinogen concentrate versus placebo for treatment of postpartum haemorrhage: study protocol for a randomised controlled trial. Trials 2015;16:169. http://dx.doi.org/10.1186/s13063-015-0670-9
43. Ducloy-Bouthors AS, Mignon A, Huissoud C, et al. Fibrinogen concentrate as a treatment for post-partum haemorrhage-induced coagulopathy: a study protocol for a randomized multicentre controlled trial. The FIbrinogen in haemorrhage of DELivery (FIDEL) trial. AnaesthCrit Care Pain Med 2016;35:293-8. http://dx.doi.org/10.1016/j.accpm.2015.10.011
44. de Lange NM, Lancé MD, de Groot R, et al.Obstetric hemorrhage and coagulation: an update. Thromboelastography, thromboelastometry, and conventional coagulation tests in the diagnosis and prediction of postpartum hemorrhage. ObstetGynecolSurv 2012;67:426-35. http://dx.doi.org/10.1097/OGX.0b013e3182605861
45. Karlsson O, Jeppsson A, Hellgren M.Major obstetric haemorrhage: monitoring with thromboelastography, laboratory analyses or both? Int J ObstetAnesth 2014;23:10-7. http://dx.doi.org/10.1016/j.ijoa.2013.07.003
46. Shaz BH, Dente CJ, Nicholas J, et al. Increased number of coagulation products in relationship to red blood cell products transfused improves mortality in trauma patients. Transfusion 2010;50:493-500. http://dx.doi.org/10.1111/j.1537-2995.2009.02414.x
47. Bonnet MP, Deneux-Tharaux C, Bouvier-Colle MH.Critical care and transfusion management in maternal deaths from postpartum haemorrhage. Eur J ObstetGynecolReprodBiol 2011;158:183-8. http://dx.doi.org/10.1016/j.ejogrb.2011.04.042
48. Arduini M, Epicoco G, Clerici G, et al. B-Lynch suture, intrauterine balloon, and endouterine hemostatic suture for the management of postpartum hemorrhage due to placenta previaaccreta. Int J GynaecolObstet 2010;108:191-3. http://dx.doi.org/10.1016/j.ijgo.2009.10.007
49. Affronti G, Giardina I, Epicoco G, et al.A conservative protocol for the management of postpartum hemorrhage. Evaluation of its effectiveness in high risk patients. It J GynaecolObstet 2014; 26 (1-3). http://dx.doi.org/10.14660/2385-0868-003
50. Ekelund K, Hanke G, Stensballe J, et al. Hemostatic resuscitation in postpartum hemorrhage - a supplement to surgery. ActaObstetGynecolScand 2015;94:680-92. http://dx.doi.org/10.1111/aogs.12607
51. Lethaby A, Mukhopadhyay A, Naik R. Total versus subtotal hysterectomy for benign gynaecological conditions. Cochrane Database Syst Rev 2012;(4):CD004993. http://dx.doi.org/10.1002/14651858.CD004993.pub3
52. Spahn DR, Bouillon B, Cerny V, et al.Management of bleeding and coagulopathy following major trauma: an updated

European guideline. Crit Care 2013;17:R76. http://dx.doi.org/10.1186/cc12685
53. Nardi G, Agostini V, Rondinelli BM, et al. Prevention and treatment of trauma induced coagulopathy (TIC). An intended protocol from the Italian trauma update research group. Journal of Anesthesiology and Clinical Science 2013; 2:22. http://dx.doi.org/10.7243/2049-9752-2-22
54. Pezzi M, Le Piane E, Giglio AM, Pagnotta L, Scozzafava A, Tortorella V, Sergi A, Verre M. Posterior Reversible Encephalopathy Syndrome in late postpartum eclampsia. Clin Ter. 2015;166(2):68-71.
55. Kanat M, Goksugur SB, Ozlu T, Tunckale A, Ozturk B, Ozturk FY, Altuntas Y, Suleymanoglu Y, Atmaca H, Yolcu N, Gonenc I, Delibasi T, Zuhur S, Dikbas O, Aktas G, Karagoz Y, Abdul-Ghani MA. The effect of feto-maternal blood type incompatibility on development of gestational diabetes mellitus. Clin Ter. 2014;165(2):e145-7
56. Ragusa A, Rinaldo D, Mansour M, Garsia S, Nichelatti M. "Tamponade Test" in the Management of Massive Postpartum Hemorrhage: The Use of the Rüsch Balloon. Reproductive Sciences 2009. 16(3): 222A (Supplement)